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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/748,451	12/22/2000	Xiaodong Wang	UTSD:546USD1	4000

7590 06/03/2003

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EXAMINER	
MOORE, WILLIAM W	

ART UNIT	PAPER NUMBER
1652	9

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/748,451	Applicant(s) WANG ET AL.	
	Examiner William W. Moore	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *91 and 93-124* is/are pending in the application.

4a) Of the above claim(s) *91,93-110 and 117-124* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *111-116* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of the subject matter of Group IV, renumbered claims 111-116, in Paper No. 8 filed March 18, 2003, is acknowledged. Examination of the subject matter of Group IV stated in the restriction requirement, Paper No. 6 mailed August 27, 2002, is directed to nucleic acid sequences that encode the generic DFF40 DNA fragmentation factor polypeptides of claims 111-115 and the specific DFF40 DNA fragmentation factor of claim 116. In telephonic discussions on May 19 and 30, 2003, between the examiner and Applicant's counsel it was agreed that Applicant had intended that claims 111-115 describe nucleic acid sequences encoding the polypeptides indicated in the claims, rather than polypeptides *per se*, and that the restriction requirement had, at page 2, classified the claimed subject matter in Class 536, subclass 23.1, i.e., as nucleic acid sequences. Claims 91, 93-110 and 117-126 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 111-115 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 111-115 describe genera of nucleic acid sequences encoding human DFF40 DNA fragmentation factor polypeptides that may differ from the amino acid sequence of the human DFF40 polypeptide disclosed in SEQ ID NO:2 in regions beyond randomly-

chosen arrays of 20, 30, 50, 50 or 100 contiguous amino acids therein. Nucleic acids having sequences which are isocoding with SEQ ID NO:1, such the nucleic acid sequences described by claim 116, are not subject to this rejection. Claims 111-115 are rejected for lack of an adequate written description because the specification fails to exemplify or describe the preparation of nucleic acids having sequences encoding the divergent DFF40 polypeptides of claims 111-115. These rejected claims reach a myriad of nucleic acid sequences encoding generic DNA fragmentation factor polypeptides that may differ substantially from the amino acid sequence of SEQ ID NO:2, yet neither the claims nor the specification describe where the differences occur or what such differences might be, nor how to distinguish a divergent, generic, human DFF40 DNA fragmentation factor amino acid sequence from a non-human DFF40 DNA fragmentation factor amino acid sequence. The requirement of claim 115 that a human DFF40-encoding nucleic acid sequence preserve an array of 100 contiguous amino acids somewhere within the overall sequence of SEQ ID NO:2 does not prevent all of the other, flanking, 238 amino acids in diverging from the disclosed sequence ,and the specification discloses no allelic variants of the nucleic acid sequence set forth in SEQ ID NO:1, thus the artisan cannot identify another encoded, divergent, human DFF40 amino acid sequence on the basis of the instant disclosure. The specification cannot otherwise disclose or suggest how other nucleic acids may be prepared to encode divergent human DFF40 DNA fragmentation factor amino acid sequences that can retain the cellular activity exhibited by the disclosed human DFF40 protein, thus meet the inherent functional limitation of claims 111-115. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification furnishes no relevant

identifying characteristics of human DFF40 polypeptides diverging at all but 20, 30, 50, 100, or more, amino acid sequence positions from the sequence of SEQ ID NO:2.

In addressing the issue of whether the disclosure of the molecular structure of a single species of polypeptide can adequately describe the molecular structures of other species of polypeptides defined mainly by functional similarity, the Court of Appeals for the Federal Circuit held that a claimed invention must be described with such "relevant identifying characteristic[s]" that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Indeed, the claims rejected herein are, like the claims invalidated by the appellate panel in *University of California v. Eli Lilly*, designed to embrace other, as yet unknown, DFF40 DNA fragmentation factors. Nothing demonstrates that, at the time the specification was filed, Applicant was "able to envision" enough of the structure of any of these undisclosed generic proteins to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The specification's treatment of the claimed subject matter is considered to be entirely prospective where skilled artisans in the relevant field of molecular biology could not predict the structure, or other properties, of the generic DFF40 DNA fragmentation factor polypeptides of claims 111-115.

Claims 111-115 are rejected under 35 U.S.C. §112, first paragraph, because the specification is not enabling for nucleic acid sequences encoding human DFF40 DNA fragmentation factors having an amino acid sequence that diverges from the amino acid sequence of SEQ ID NO:2 by amino acid substitutions, deletions and insertions, or combinations thereof at as many as 90%, or even 70%, of the amino acid positions within SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 111-115 contemplate preparation of very large genera of nucleic acids having sequences wherein codon alterations permit arbitrary assignments of any or all of amino acid substitutions, additions or deletions, see pages 17-18 of the specification, in the disclosed amino acid sequence of the human DFF40 DNA fragmentation factor set forth in SEQ ID NO:2. Even the requirement of claim 115 that a human DFF40-encoding nucleic acid sequence preserve an array of 100 contiguous amino acids somewhere within the overall sequence of SEQ ID NO:2 permits all of the other, flanking, 238 amino acid positions therein, 70% of the DFF40 amino acid sequence. The suggestion at page 17 of the specification a signal peptide be deleted is inappropriate for a polypeptide, like the DFF40 fragmentation factor, with intracellular function and the specification's proposals, page 22, that domains of DFF40, DFF45 and ICAD polypeptides of different species of animals be "switched" to form chimeric polypeptides cannot support the claim limitation "human" and provides no guidance as to what domains may be spliced, nor where the splicing should occur, in order to conserve the capacity of a human DFF40 to be readied for its activity by the folding of its amino acid sequence by its human, DFF45, chaperonin, a semi-regulatory step within the cell, or to sustain its DNA fragmentation activity.

Claims 111-115 are rejected for lack of enablement under the first paragraph of the statute because the specification cannot support the breadth of the proposed modifications contemplating the preparation of nucleic acid sequences encoding polypeptides having amino acid modifications of the amino acid sequence of SEQ ID NO:2 at 238 or more positions therein, where the modifications include amino acid insertions, deletions, or substitutions anywhere, in any combination or any pattern, in regions that flank an array of 100 in claim 115, 30 in claim 114, 50 in claim 113, 20 in claim 112, or fewer in claim 111, contiguous amino acids at unspecified locations within SEQ ID NO:2, yet provide a DNA fragmentation factor that will form a complex with the DFF45 factor and function in

the nucleus of a cell. Indeed, neither Applicant's specification nor the prior art made of record herewith can identify, taken together, such great numbers of positions in the amino acid sequence of SEQ ID NO:2 that can be altered, nor teach the nature such alterations, which will permit the divergent polypeptide to form a complex with the DFF45 factor and to also support DNA fragmentation activity. Mere sequence perturbation cannot enable the design and preparation of nucleotide sequences encoding a myriad of divergent DFF40 fragmentation factors and provide the public with a useful nucleotide sequence encoding a factor retaining native functions.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). The standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability of factors involved in physiological activity of small peptide hormone); see also, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (functional equivalency of divergent gene products not supported by disclosure only of a single B-cell growth factor allele). The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997).

The Federal Circuit has also considered whether definitional statements might enable a claim scope argued to extend beyond a disclosed gene product having its native amino acid sequence to embrace another, specific, variant gene product encoded by a specifically-altered DNA sequence. *Genentech, Inc. v. The Wellcome Found. Ltd.*, 29 F.3d 1555, 31 USPQ2d 1161 (Fed. Cir. 1994). The court held that only a narrow structural and functional definition was enabling precisely because the sweeping definitions of scope in the patent specification could not reasonably have been relied upon by the PTO in issuing the patent. *Genentech*, 29 F.3d 15 at 1564-65, 31 USPQ2d at 1168. Applying the "*Forman*" factors discussed in *Wands, supra*, to Applicant's disclosure, it is apparent that:

> a) the specification lacks adequate, specific, guidance for preparing nucleic acid sequences encoding altered human DFF40 DNA fragmentation factors diverging at 238 or more amino acid positions from the amino acid sequence set forth in SEQ ID NO:2 embraced by claims 111-115,
>
> b) the specification lacks working examples wherein any nucleic acid sequence has been prepared that encodes altered human DFF40 DNA fragmentation factors diverging at even one amino acid position from the amino acid sequence set forth in SEQ ID NO:2,
>
> c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,
>
> d) unpredictability exists in the art where no members of the class of DFF40 DNA fragmentation factors capable of forming a complex with a DFF45 polypeptide and supporting nuclear DNA fragmentation activity have had any native amino acid sequence positions specifically identified for concurrent modification.

Thus the scope of subject matter embraced by a phrase, "DNA fragmentation factor . . . comprises 20[or 30, or 50, or 100] contiguous amino acids of SEQ ID NO:2", is unsupported by the present specification even if taken in combination with teachings available in the prior art.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 111-116 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The independent claim 111 is indefinite in reciting, "isolated polypeptide encoding a human DFF40 fragmentation factor", because one polypeptide cannot encode another. Polypeptides are neither replicated, transcribed, nor translated on the basis of any code inherent in their structure – wherein amino acids joined one to another in series by peptide bonds – and are instead recognized in the relevant art of molecular biology to be encoded by nucleic acids sequence. Thus, artisans reading the specification at, e.g., page 4 lines 23-25, must regard the intended invention as "an isolated nucleic acid" or, equivalently, "an isolated polynucleotide", encoding a human DFF40 DNA fragmentation factor. Claims 112-116 are included in this rejection because they depend from claim 111 but do not correct its ambiguous description. Deleting the term "polypeptide" in claim 111 and replacing it with "nucleic acid", or with "polynucleotide", will overcome this rejection.

Allowable Subject Matter

Claims 111-116 are allowable over the prior art of record herein. Enari et al., 1998, Nature, Vol. 391, pages 43-40, made of record with Applicant's Information Disclosure Statement, is the earliest publication of isolation and sequence determination of a nucleic acid encoding a mammalian caspase-activated DNase, the murine CAD, a homologue of the human DFF40. While the mouse cDNA isolated by Enari et al. encodes an amino acid sequence, see Figure 5d at page 47, sharing 79.2% amino acid sequence identity with the amino acid sequence of SEQ ID NO:2 herein and comprising an array of 22 contiguous amino acids identical to those between positions 246 through 262, inclusive, of SEQ ID NO:2 herein, it is inapplicable as prior art to claims 111-116 herein under 35 U.S.C. §103(a). This is because, just as skilled artisans cannot predict where divergent human nucleic acid sequences might a change in the amino acid sequence of SEQ ID NO:2 herein on the basis of Applicant's disclosure, one of ordinary skill in the art at the time the invention was made would have had no basis in teachings of Enari et al. for predicting the

order of codons present in a human DFF40 nucleic acid sequence or its encoded amino acid sequence, nor predict whether or not any region of the murine CAD would have an array of contiguous amino acids identical to a region of SEQ ID NO:2. The International Application of Halenbeck et al., WO 99/10501, is made of record as relevant to Applicant's disclosure because it discloses, page 38, a nucleic acid sequence encoding a human DFF40, termed CPAN by Halenbeck et al., and its encoded amino acid sequence which is 99.9% identical to that of SEQ ID NO:2 herein, differing only at position 196 in both sequences. The PCT publication is not prior art under 35 U.S.C. §102(a) because it was made after Applicant's priority date for the subject matter claimed herein. It is not prior art under 35 U.S.C. §102(e) in view of the 2002 Amendments to the American Inventors Protection Act of 1999 because the three U.S. provisional applications cited as priority documents on the face of the PCT publication and filed nine, or four, months before Applicant's priority date are, were filed before November 29, 2000.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at 703.308.3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. The examiner's direct fax phone number is 703.746.3169. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
May 30, 2003